Remarks

Rejections under 35 U.S.C. 112

Claims 1, 7 and 14 were rejected as allegedly indefinite. Claims 1, 7 and 14 are amended as suggested by the Examiner to delete the term "including" and the included polymers (since they are clearly encompassed within the general terms) from the Markush group defined therein.

The Examiner alleged that recitation of diketopiperazine in the Markush group in claims 1, 7 and 14 render the claims indefinite. The applicants respectfully disagree, but have amended the claims to refer specifically to an "excipient" rather than "a material" and to break down the Markush group into two parts, diketopiperazines and synthetic polymers (page 5, line 23). Claims 1, 7 and 14 recite a dry powder formed of a drug and **an excipient** (see page 5, line 3, for example) as defined in the Markush group of the claims. Diketopiperazines are included in the Markush group as an excipient suitable for forming the dry powder. The diketopiperazines are not the drug, but the carrier. Diketopiperazines have been used as excipients in the art of drug delivery (see, e.g., U.S. Patent No. 5,503,852 to Steiner et al.).

Rejections under 35 U.S.C. 102

Claims 1-4, 6-11, 13-17 and 19 were rejected as anticipated under 35 U.S.C. 102(b) by U.S. Patent No. 5,690,954 to Illum ("Illum"). The applicants respectfully traverse the rejection if it is applied to the claims as amended.

The claimed invention

Claims 1-19, as amended, are drawn to a composition for the nasal administration of a drug in a dry powder form **consisting essentially of particles** having an average particle size of between 10 and 20 microns, formed of drug and a synthetic polymer (page 5, line 23) or diketopiperazine excipient in a dosage formulation suitable for administration to the nasal region

and a method of using the composition. Natural polymers have been deleted from the claims. A critical aspect of the formulation is the range of its particle size between 10 and 20 microns (p. 2, lines 19-23). A size below 10 microns could cause the composition to pass into the pulmonary region or mouth, which would result in a low efficient delivery of the drug and cause undesirable side effects with certain type of drugs, e.g., bitterness in the case of an antihistamine. A size range between 10 microns and 20 microns allows a lower dosage to be administered, avoids or ameliorates the systemic side effects such as somnolescence due to lower dosage, and avoids the problem with bitter taste for drugs such as antihistamine (p. 2, lines 2-16).

Illum

Illum describes a drug delivery system including a plurality of microsphere particles containing an active drug and a penetration enhancer associated with each particle (col. 4, lines 5-12) which increases the bioavailability of the drug. Representative uptake enhancers are phospholipids and lysophosphatidyl compounds (col. 4, lines 22-30). The microspheres are formed of a natural polymer such as a starch (col. 6, line 17) or any one of gelatin, casein, dextrans, alginate, ararose, albumin, collagen, chitosan, polyvinylacetate, and hyaluronic acid esters (col. 6, lines 17-20), which gels in contact with the mucosal surface (col. 6, lines 15-16). The microspheres have a size between 10 to 100 microns (col. 6, line 13).

Summary

The claims require:

a dry powder form comprising microparticles

the microparticles having an average particle size of between 10 and 20 microns

the microparticles consisting essentially of the drug and an excipient

the excipient being either

diketopiperazines or

a synthetic polymer: poly(hydroxy acids), polyanhydrides, polyesters, polyorthoesters, polyamides, polycarbonates, polyalkylenes, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, poly vinyl chloride, polystyrene, polysiloxanes, polymers of acrylic and methacrylic acids, polyurethanes and co-polymers thereof, celluloses, poly(butic acid), poly(valeric acid), poly(lactide-co-caprolactone), and copolymers thereof.

✓ Illum discloses particles including drug, hydrogel and enhancer; and a size range of up to 100 microns.

Illum does not discloses any of the claimed synthetic polymeric materials or diketopiperazines.

Accordingly, the claims are novel over Illum.

Rejections under 35 U.S.C. 103

Claims 5, 12 and 18 were rejected as obvious under 35 U.S.C. 103 over Illum in view of U.S. Patent No. 6,136,835 to Camden ("Camden"). The applicants respectfully traverse the rejection if it is applied to the claims as amended.

Illum

The claims are also non-obvious over Illum.

None of these materials are a dry powder. This is important because Illum is trying to enhance penetration - using the combination of an enhancer, a phospholipid, in a hydrogel, and achieves tremendous results with certain drugs to be delivered. See, for example, the data in Figure 6. The enhancer is critical to uptake.

In contrast, applicants use the selection of a very narrow size range, between 10-20 microns, to achieve the small result. The synthetic polymers are in the form of a dry powder, not a hydrogel. There is no enhancer (note the use of the term "consisting of"). The term "consisting essentially of" has been construed by courts to exclude other essential elements other than the ones defined in the claims (see, for example, PPG Industries v. Guardian Industries Corp., 156 F.3d 1351, 48 USPQ2d 1351 (Fed. Cir. 1998)). Illum's particles are much larger - see col. 6, line 53 (33 microns); col. 7, line 1 (40-60 microns); col. 7, line 20 (43 microns); col. 7, line 31 (70 microns); col. 7, line 42 (60 microns). Illum teaches that the enhancer is the critical element. Applicants use size and inert excipient instead.

Camden

Camden describes a formulation of 2-(2,4-difluorophenyl)-1,3-bis(1H-1,-triazol-1-yl)propan-2-ol or derivatives thereof as a drug for the treatment of viral infections (col. 3, lines 20-43). The formulation may include a potentiator (col. 11, line 51). A bis-diketopiperazine derivative is listed in a large laundry list of potentiators (col. 13, line 31). A potentiator is defined as an immunomodulator that acts on the immune system (col. 11, lines 51-55). The drug can be formulated into a powder formulation, with a solid carrier, having a particle size of less than 100 microns, preferably less that about 50 microns (col. 16, lines 64-67). Solid carriers can be lactose, sucrose, gelatin, agar and bulk powders (col. 15, lines 17-19). Camden does not teach a dry powder formulation comprising the drug and the bis-diketopiperazine alone without a solid carrier. Camden does not recognize or teach the size range of 10 to 20 microns for delivery of the formulation to the desired nasal region.

There is nothing in either Illum nor Camden that would lead one of skill in the art to combine Illum with Camden. Indeed, Illum teaches away from the use of 10-20 micron particles

and teaches that one must use an enhancer. Camden teaches that one particular diketopiperazine may be bioactive, although there is no evidence of this assertion and it is contradicted by the prior publications on diketopiperazines used in drug delivery, where inertness was a requirement to use of the material for drug delivery. Both Illum and Camden teach away from using only an inert carrier. Accordingly, Illum in view of Camden, fail to disclose every element of the composition and method of using the composition defined in any of claims 1-5, 7-12, and 14-18, and the motivation for one of ordinary skill in the art to make and use the composition defined in any of claims 1-5, 7-12, and 14-18.

Even if one of ordinary skill in the art were motivated to combine Illum and Camden, Illum and Camden, if combined, still fail to make obvious claims 1-5, 7-12, and 14-18, as amended. The claims as amended, require the dry powder to consist essentially of particles having an average size between 10 and 20 microns formed of a drug and a material defined therein. As such, Illum in view of Camden would not lead one of ordinary skill in the art to have a reasonable expectation of success of the subject matter defined in any of claims 1-5, 7-12, and 14-18.

U.S.S.N.: 09/766,362
Filed: January 19, 2001
AMENDMENT AND RESPONSE TO OFFICE ACTION

Allowance of claims 1-5, 7-12, and 14-18 is therefore earnestly solicited.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 431,28

Dated: August 21, 2003
HOLLAND & KNIGHT LLP
2000 One Atlantic Center
1201 W. Peachtree Street
Atlanta, GA 30309-3400
(404) 817-8473
(404) 817-8588 (fax)

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the enclosed Response to Office Action and all documents shown as being attached is being facsimile transmitted to Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Date: August 21, 2003

Peggy Bailey

ATL1 #588956 v1